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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/088,293 | 10/15/2002 | Pascale Serror | 045636-5055 | 1179 |
| 9629 | 7590 | 06/02/2004 | EXAMINER | |
| MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004 | | | KATCHEVES, KONSTANTINA T | |
| | | ART UNIT | | PAPER NUMBER |
| | | | | 1636 |

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/088,293 | SERROR ET AL. | |
| | Examiner | Art Unit | |
| | Konstantina Katcheves | 1636 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 March 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 11-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 11-20 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 15 March 2002 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 10/15/2002.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

Claims 11-20 are pending in the present application.

Specification

The attempt to incorporate subject matter into this application by reference to the following is improper: (1) the sequence pIP5O1 is described by Brantl et al. (*Molecular Microbiology*, 3501-3510 (1992)) as disclosed on page 5 of the specification; (2) the insertion sequence IS1233 is described by Walker et al. (*J. Bacteriol.*, 176, 5330-5340, 1994) as disclosed on page 11 of the specification; (3) the insertion sequence named IS1201 demonstrated by Taillez et al. (*Gene*, 145, 75-79, 1994) as disclosed on page 11 of the specification; and (4) the replication system pVE6002 described in Biswas et al. (*J. Bacteriol.*, 175, 3628-3635 (1993)), Maguin et al. (*J. Bacteriol.*, 178, 931-935 (1996)) and WO93/18164 as disclosed on page 3 of the specification.

MPEP 608.01(p) states:

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate “essential material” by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. “Essential material” is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates “essential material” by reference, or (4) a foreign application. . . . Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph.

The incorporation by reference of the subject matter set forth in the disclosed citations is improper because pIP5O1, IS1201 and IS1233 are essential subject matter necessary to adequate

describe the claimed invention. Moreover, no statement specifically incorporating the subject matter is found. Applicant merely refers to the above publications.

Claim Objections

Claim 13 is objected to because of the following informalities: Claim 13 contains two periods. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maguin et al. (J. of Bacteriology Vol178 no.3 1996) in view of Gruss et al. (WO 93/18164) and Sasaki et al. (EP 0 603 416). Applicant cites each of these references in the specification as prior art. See *In re Nomiya* 509 F.2d 566, 184 USPQ 607, 611 (CCPA 1975) (stating that when applicant asserts something is prior art, it can be used as against the claims).

The invention of the instant claims is drawn to a method of introducing a modification of the genome of a *Lactobacillus delbrueckii* comprising introducing a related replication system to pIP50 as a thermosensitive vector into the bacterium. Giving the claims their broadest reasonable interpretation, any replication system capable of modifying the modification of *Lactobacillus delbrueckii* is related to pIP501.

Maguin et al. teach thermosensitive mutant vectors comprising the pVE6002 mutant replicon used in a method wherein gram-negative lactic acid bacteria, *Lactococcus lactis*, are modified using thermosensitive vectors. The plasmid is introduced into the bacteria at a permissive temperature. These bacteria are then cultured at a temperature which non-permissive for the replication of the plasmid. See Maguin et al. page 931, column 2 and page 933, column 2. Maguin et al. also teach that the thermosensitive plasmid has a broad application in gram-positive organisms. See page 934, column 2. See also specification page 3. Maguin et al. fail to teach a selective marker and *Lactobacillus delbrueckii* as a host strain.

Gruss et al. teach thermosensitive vectors like those disclosed by Maguin et al. comprising the pVE6002 mutant replicon used in a method wherein gram-negative lactic acid that can be used in the transformation of a variety of lactic acid bacteria including *Lactobacillus delbrueckii subs. bulgaricus*. See Specification, page 3 and Gruss et al. abstract and figures. Gruss et al. fail to teach a selective marker.

Sasaki et al. teach a vector which allows integration of sequences into the chromosome of *Lactobacillus Delbruecki* with the plasmid pAMβ1 and teaches the use of this plasmid in a method to integrate a modification into the chromosome of *Lactobacillus delbrueck*. A selection marker, erythromycin resistance, was inserted into a fragment homologous to a region of the chromosome of *Lactobacillus delbrueckii* by using the plasmid pAMβ1 as a vector for the integration, by homologous recombination, of the insert from the plasmid into the chromosomal DNA. See abstract and page 4. See also Specification, page 2. Sasaki et al. fail to teach a thermosensitive vector.

The invention claimed would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a modification into the genome of *Lactobacillus delbrueckii* using a thermosensitive replication system related to pIP501 such as the either the integrative vectors of Sasaki et al., Maguin et al. or Gruss et al. Sasaki et al. specifically teach the modification of *Lactobacillus delbrueckii* and a selection marker integrated into the genome of a host. Maguin et al. and Gruss et al. teach thermosensitive vectors to modify gram-negative bacteria, a class of bacteria to which *Lactobacillus delbrueckii* belongs. Maguin et al. do not specifically include *Lactobacillus delbrueckii* in their method using a thermosensitive vector. However, Applicant admits that Gruss et al. teach the same thermosensitive vectors as Maguin et al. used in a variety of gram-negative bacteria including *Lactobacillus delbrueckii subsp. bulgaricus*. The disclosures of Gruss et al. and Maguin et al. wherein they teach the method of modifying the genome of *Lactobacillus delbrueckii* with an insertion sequence provide ample motivation for one of skill in the art to integrate nucleic acid into the genome of the claimed bacteria. Moreover, the disclosures of Sasaki et al. wherein a selection marker has been inserted into the genome of *Lactobacillus delbrueckii* provides motivation to include a selection marker in order to select for bacteria having the integrated sequences and provides evidence of a reasonable expectation of success in addition to the disclosures of Gruss et al. and Maguin et al. for the chromosomal modification of *Lactobacillus delbreuckii*. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-17, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is established by 35 U.S.C. 112, first paragraph which states that the: “*specification* shall contain a written description of the invention. . [emphasis added].” A specification must convey to one of skill in the art that “as of the filing date sought, [the inventor] was in possession of the invention.” See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in “possession” of the invention claimed by describing the invention with all of its claimed limitations “by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention.” See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The claims are drawn to a plasmid comprising the pIP501 replication system, “or a related replication system.” This is a broad genus of replication systems. These are genus claims that encompass a wide array of molecules. The instant claims are drawn to replications systems which have certain common functional characteristics. However, the specification fails

to disclose how these replication systems are related. What are the functional and structural characteristics that tie these related replication systems together. The specification also does not disclose representative replication systems that are related to pIP201. Thus, the specification does not describe the complete structure of a representative number of species. Moreover, the specification fails to describe a representative number of species in terms of common partial structure or relevant identifying characteristics. Absent teachings and guidance as to the structure-function relationship of these related replication systems, the specification does not describe the claimed genus in such full, clear, concise and exact terms so as to indicate that Applicant had possession of the broad genus of related replication systems at the time of filing of the present application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the language “integration into a bacterium” and the preamble states “a modification of the genetic material of a bacterium.” The question is raised whether “integration” means into the genome of the bacterium or is the plasmid episomally expressed in the bacteria.

Claim 12 is inconsistent. Step (b) requires the multiplication of the bacteria under conditions which permit replication of the plasmid. Step (c) requires the multiplying of the

bacteria under conditions which prevent the replication and/or maintenance of the plasmid.

Claims are given their broadest reasonable interpretation. Moreover, there is no article between step (b) and step (c). Thus, it is unclear whether step (c) must come after step (b), whether a skilled artisan may select a method comprising step (a) and either step (b) or step (c).

Steps (b) and (c) of claim 12 are also inconsistent in the limitations they recite because step (b) permits the replication and maintenance while step (c) prevents the replication and/or maintenance. This raises the question whether Applicant intends to prevent both the replication and maintenance in step (c) both of which are promoted in step (b).

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the modification of the genetic information in the chromosome of *Lactobacillus delbrueckii*. The steps (b) and (c) in the method requires multiplying the bacteria under conditions which permit replication and maintenance of the plasmid and conditionals which prevent the replication and/or maintenance of the plasmid. Neither of these steps involves the modification of genetic information.

Claim 18 recites language which state that an insertion sequence is introduced into the “nucleus” of bacterial cells. Bacteria are prokaryotes. The lack of a nucleus is one of the characteristics which distinguishes prokaryotes from eukaryotes. Therefore, this language renders claim 18 unclear.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The instant claim recites a method of modifying the chromosome of a bacterial cell

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and recites a step of introducing an insertion sequence into the cell, yet fails to recite a step of modifying the chromosome. Therefore, there is no nexus between the introduction of the insertion sequence and the modification of the chromosome.

Claim 18 appears to recite a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. The metes and bounds of this Markush group is indefinite because it is unclear if the members of this group are mutually exclusive. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Konstantina Katcheves
Examiner
Art Unit 1636